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Preparation and Evaluation of Sulfacetamide Sodium Ocusert for Controlled Drug Delivery

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ABSTRACT

The intent of this research was to formulate and evaluate controlled release ocusert of sulfacetamide sodium for the treatment of bacterial conjunctivitis. Ocusert is a sterile preparation having drug as dispersion or as solution in the polymeric base. Prepared Ocuserts were formulated using hydroxyl propyl methyl cellulose K-15 and Ethyl cellulose as polymers at various concentrations and combinations. Polymeric Films were prepared by mercury casting method using different ratios of polymers. Selected physiochemical properties such as thickness, weight, percentage moisture absorption, and *in-vitro* release and sterility studies of sulfacetamide sodium ocusert were studied and reported that prepared ocusert resolved the problems of poor bioavailability, frequent dosing and wastage of active ingredient.

Keywords: Hydroxypropyl methyl cellulose K-15, ocusert, sulfacetamide sodium

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INTRODUCTION

The human eye is a body part that reacts to light. As a sense organ, the mammalian eye allows vision, perception and vision including colour differentiation and the perception of depth[1]. The main purpose of formulating ocusert is to enhance ocular bioavailability by increasing the corneal contact time. Fewer administrations provide patient compliance. Bacterial conjunctivitis or pink eye is a common, self-limiting condition that is typically caused by adenovirus[2].

Topical application of drug to the eye is the most popular and well-accepted root of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drug is, however, very poor due to efficient protective mechanisms of the eye[3]. Many ophthalmic drug delivery systems are available these are classified as conventional and non-conventional (newer) drug delivery systems. Most commonly available ophthalmic preparations are eye drops and eye ointments which are instilled into the cal-de-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage[4]. The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix[5].

Ocusert is the delivery system which is determined for its most logical aspects. The main objective of this delivery system is the increased residence time in the eye. This delivery system is the preferred route to deliver the drug as it provides sustained and controlled release of the drug to the desired site of action[6].

Sulfacetamide sodium is a sulphonamide antibiotic with inhibitive activity towards bacteria and broad-spectrum activity towards most gram-positive and many gram-negative bacteria's[7]. It is used for the treatment of bacterial conjunctivitis and other superficial ocular infections due to susceptible Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus (viridans group), Haemophilus influenzae, Klebsiella species, Enterobacter species[8]. However, many strains of different species might be resistant[9]. Wide distribution of sulphonamides is observed

throughout the body. Enhanced levels are achieved in synovial, pleural, ocular and peritoneal fluids[10]. Sulphonamides act as competitive inhibitors of p-amino benzoic acid in the metabolism cycle of folic acid[11]. The inhibition process is obligatory in these organisms for the production of folic acid.

MATERIALS AND METHODS

Sulfacetamide sodium was procured from Ramson Remedies Pvt. Ltd., Amritsar (Punjab). PVA, HPMC and di-butyl phthalate were purchased from Sigma Aldrich. Chloroform and hydrochloric acid were purchased from Merk. All chemicals were of analytical grade.

Preparation of ocuserts

Ocusert of sulfacetamide sodium was prepared in following three steps-

i. Preparation of the drug reservoir,

ii. Preparation of the rate controlling membrane and

iii. Sealing of the rate controlling membranes with the reservoir.

i. Preparation of the drug reservoir

The Sulfacetamide sodium ocular inserts were prepared by solvent casting method. The required quantity of polymer and plasticizer were weighed and dissolved in double distilled water (20 ml) and the mixture was heated at 60°C on a water bath until the entire polymer was dissolved. The drug material was calculated mathematically as per clinical dose. Weighed amount of Sulfacetamide sodium (# 400) was added and stirred for 6 hours at 40°C on magnetic stirrer to get uniform dispersion. The solution was sonicated until uniformity was obtained. After complete mixing, the casting solution (1 ml) were poured into glass rings (8 mm) which were lying on the mercury as substrate in the petri-dish and then placed in the hot air oven for 48 hours at 40ºC. The petri-dish was covered with inverted funnel to ensure the slow evaporation of solvent. The dried films were then separated from glass rings carefully with the help of surgical blade. The prepared reservoirs were then stored in desiccators under ambient condition[4].

Preparation of the rate controlling membranes

A weighed quantity of polymer was dissolved in 5 ml of ethanol to obtain polymeric solution. Stirring was continuously maintained until the clear solution was obtained. These solutions were poured into glass ring (8 mm) which was lying on the mercury as substrate in the petri-dish and then remaining solution (2 ml) was placed in the hot air oven for 48 hours at 40ºC. The dried films were removed as separated earlier[12].

Sealing of the films

The drug reservoir was sandwiched in between the two rate controlling membranes and sealing was done by applying chloroform on the edges of the rate controlling membrane so that both the sides of the drug reservoir were sealed to control the release from periphery. The ocular inserts were stored in an air tight container[13].

Table 1: Composition of the reservoir films

S. No.	Ingredients	F1A	F2A	F3A	F4A
1	Sulfacetamide sodium (mg)	20	20	20	20
2	Polyvinyl alcohol (PVA)	0.6%	0.7%	0.8%	0.9%
3	Hydroxypropyl methyl cellulose K-15(HPMC K-15)	0.6%	0.7%	0.8%	0.9%
4	Dibutyl phthalate (% w/w of polymer)	30%	30%	30%	30%
5	Double distilled water (ml)	15	15	15	15

Table 2: Composition of rate controlling membranes

S. No.	Ingredient	F1B	F2B	F3B	F4B
1	Ethyl cellulose	1.2%	1.4%	1.6%	1.8%
3	Dibutyl phthalate (% w/w of polymer)	30%	30%	30%	30%
4	Ethanol (ml)	15	15	15	15

Table 3: Final formulations prepared after sealing:

Formulations	Drug reservoir + rate controlling membrane
F1	F1A + F1B
F2	F1A + F2B
F3	F1A + F3B
F4	F1A + F4B
F5	F2A + F1B
F6	F2A + F2B
F7	F2A + F3B
F8	F2A + F4B
F9	F3A + F1B
F10	F3A + F2B
F11	F3A + F3B
F12	F3A + F4B
F13	F4A + F1B
F14	F4A + F2B
F15	F4A + F3B
F16	F4A + F4B

Characterization of ocular inserts of Sulfacetamide sodium

Physical evaluation

Ocusert film was evaluated for physical evaluations such as properties, shape, colour, texture and appearance[14].

Uniformity of thickness

The thickness of the insert was determined using a Micrometre screw gauge. Three randomly selected inserts were tested for their thickness at five separate points of each inserts for each formulation[15].

Uniformity of weight

Ocular insert was weighed individually using digital balance. The mean weight of the insert was noted[16].

Drug content

The ocusert from each formulation was dissolved or crushed in 10 ml of isotonic phosphate buffer (pH 7.4) in a beaker and were filtered into 25 ml volumetric flask and the volume was made up to the mark with buffer. One ml of the sample was withdrawn and the absorbance was measured by UV-Visible spectrophotometer at 271 nm after suitable dilutions[17].

% Moisture absorption

This was done to check the physical stability or integrity of the films at humid condition. The films were weighed and placed in desiccators containing 100 ml of saturated solution of aluminium chloride and 80% humidity was maintained. After three days the films were taken out and reweighed[18]. The % moisture absorption was calculated using the formulae:

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

% Moisture Loss

This was carried out to check the integrity of the films in dry condition. The films were weighed and kept in desiccators containing anhydrous calcium chloride[19].

Folding endurance

Folding endurance was determined by repeatedly folding a small strip of the film at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. A mean of three readings were recorded[20].

Surface pH

The inserts were allowed to swell in closed petri dish at room temperature for 30 min in 0.1 ml of double distilled water and placed under digital pH meter to determine the surface pH. The pH meter was calibrated before each use with standard pH 4 and 7 buffer solutions[21].

Swelling index

Three ocuserts were weighted and placed separately in beakers 4 ml of simulated tear fluid. After a period of 5 minutes, ocuserts were removed and the excess water on the ocuserts was wiped and weighed[22]. The % swelling index was calculated as:

(Weight of swollen insert after time – original weight of insert at zero time) × 100

In vitro diffusion study

In-vitro release studies were carried out using bi-chambered donor receiver compartment model (Franz diffusion cell). The diffusion cell membrane (pre-hydrated cellophane) was tied to one end of the open cylinder, which acted as donor compartment. The ocular insert was placed on a dialysis membrane which was in contact with receptor medium comprising of 22 ml of STF (pH=7.4). The content of the receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at $37^0 \pm 0.5^0$C. The receptor medium was stirred continuously at 20rpm to simulate blinking action of eyelids. At specific time interval, 1ml aliquot of the solution was withdrawn and replaced with fresh STF and required dilutions were made. The aliquot was analysed for drug content was analysed using UV Spectrophotometer at 256 nm against reference standard using simulated tear fluid as blank[23].

Mechanism and kinetics of drug release from an ophthalmic insert

In order to understand the mechanism and kinetics of drug release, the results of *in vitro* drug release study were fitted with various kinetic equations like zero order (%drug release vs. time), first order (log% unreleased vs. time), and Higuchi matrix (% release vs. square root of time)[24].

Sterility studies

All ophthalmic preparations should be sterile therefore the test for sterility is very important evaluation parameter. The sterility test was performed according to Indian Pharmacopoeia. Direct inoculation method was used 2 ml of prepared Sulfacetamide sodium ocusert solution was removed with a sterile pipette or with a sterile syringe or a needle. The test liquid was aseptically transferred to fluid thioglycolate medium and soyabean-casein digest medium separately. The liquid was mixed with the media. The inoculated media were incubated for not less than 14 days at 30°C to 35°C in the case of fluid thioglycolate medium and 20°C to 25°C in the case of soyabean-casein digest medium[25].

RESULTS

Physical evaluation

Table 4: Physical evaluation of prepared ocusert

Properties	Results observed
Shape	Circle
Colour	White
Appearance	Uniform (no visible cracks)
Texture	Smooth

Uniformity of thickness

The average thickness of Ocuserts was between 0.12 ±0.013mm to 0.19±0.072mm. There were no marked variations in the thickness of Ocuserts within each formulation indicating uniform behaviour of film throughout the process.

Uniformity of Weight

The average weights of Ocuserts were found to be in the range of 6.1 mg to 7.2 mg. The uniformity of weight of Ocusert indicated good distribution of the drug, polymer and plasticizer.

Swelling Index

The polyvinyl alcohol (PVA) and Hydroxypropyl methyl cellulose (HPMC) are hydrophilic polymers and are soluble in water. Due to hydrophilic nature of PVA and HPMC it was expected to absorb water. Because of this swelling index test was carried out. The result showed that there was no significant variation in the water absorbs properties of formulations. Swelling index was found in the range of 1.45 to 2.80%.

Folding Endurance

The folding endurance was measured for all formulations manually. It was found in the range of 77 to 98. This test reflects the flexibility of ocuserts. This test ensures that the prepared ocuserts were suitable for large scale manufacture to produce long, continuous film without breaking or tearing.

% Moisture absorption

The % moisture absorption was calculated for all 16 formulations. A positive linear correlation was found between the moisture absorption capacity and the concentration of hydrophilic polymers PVA and HPMC increased the % moisture absorption also increased.

% Moisture loss

The % moisture loss was calculated for all 16 formulations. A positive linear correlation was found between the moisture absorption capacity and the concentration of hydrophilic polymers PVA and HPMC increased the % moisture loss also decreased.

Surface pH

The prepared ocular insert was subjected for measurement of pH and it was found in range of 6.8 to 7.20. The pH range of all the formulation was found near to tear fluid pH so patient compliance of ocular insert is good.

Drug content

The Drug content was found consistent in all formulations and varied from 91.45 ±0.02% and 99.78±0.01%.

Table 1: Evaluation chart of ocusert

Formulation code	Weight (mg)	Thickness (mm)	Surface pH	Folding Endurance	%Moisture absorption	%Moisture loss	Swelling Index (%)	Drug Content
F1	6.49±0.12	0.11±0.004	7.10±0.07	77±2.17	5.23±0.23	8.35±0.30	1.84±0.0108	91.45±0.02
F2	6.91±0.21	0.129±0.009	6.87±0.13	79±1.92	5.81±0.35	9.4±0.23	1.67±0.0211	94.57±0.07
F3	6.47±0.18	0.123±0.004	6.91±0.02	82±1.81	7.23±0.75	8.75±0.05	1.76±0.0107	93.50±0.03
F4	7.22±0.11	0.131±0.007	7.20±0.19	80±3.20	6.98±0.123	8.9±0.06	1.92±0.0102	92.70±0.01
F5	6.77±0.71	0.148±0.003	7.10±0.11	94±2.12	8.64±0.65	6.57±0.21	2.21±0.0126	93.67±0.08
F6	6.61±0.42	0.157±0.012	6.82±0.05	90±3.52	8.20±0.67	6.79±0.11	2.33±0.0234	97.34±0.01
F7	6.82±0.17	0.143±0.015	7.19±0.14	93±1.43	9.64±0.42	6.13±0.36	1.71±0.0241	98.34±0.08
F8	6.33±0.27	0.160±0.007	7.14±0.01	94±2.76	8.56±0.13	7.57±0.14	1.89±0.0114	97.90±0.01
F9	7.02±0.20	0.156±0.017	7.02±0.09	96±1.05	11.46±0.46	6.68±0.27	1.82±0.0113	99.40±0.04
F10	6.59±0.56	0.164±0.013	6.97±0.06	84±1.26	11.96±0.60	5.68±0.39	1.99±0.0103	99.23±0.07
F11	6.88±0.19	0.162±0.002	6.87±0.12	92±2.74	10.11±0.24	4.6±0.09	2.13±0.0321	96.89±0.02
F12	6.41±0.31	0.177±0.006	7.16±0.17	95±2.34	11.34±0.12	5.98±0.12	2.61±0.0248	93.79±0.08
F13	7.07±0.16	0.162±0.012	7.12±0.10	95±2.87	12.64±0.45	5.46±0.38	1.96±0.0108	98.01±0.03
F14	6.91±0.32	0.172±0.008	7.15±0.11	98±3.02	12.75±0.87	4.57±0.20	2.12±0.0101	99.78±0.01
F15	7.09±0.51	0.169±0.011	7.08±0.19	79±1.38	13.57±0.20	4.8±0.70	2.18±0.0111	95.78±0.05
F16	6.65±0.3	0.171±0.01	7.17±0.1	87±2.09	13.64±0.70	5.6±0.20	2.71±0.030	96.24±0.0

In vitro diffusion study

In vitro drug release of the Sulfacetamide sodium ocusert was formulated by making 16 batches (F1 to F16). Various release kinetic model such as zero order, first order, Higuchi model and Korsemeyer-Peppas release model were studied for all formulations. All formulations were seen following zero order release kinetics out of which the best formulation F9 revealed better controlled release of drug content *in-vitro* (99.5%) within 12 hrs. is shown in figure 1.

Table 5: In-vitro drug release profile of sulfacetamide sodium ocusert containing PVA, EC, HPMC K-15 (batch F9)

Time (hrs)	0	1	2	3	4	5	6	7	8	9	10	11	12
Cumulative %drug dissolved	0	6.92	16.16	25.28	34.88	46.18	49.34	57.55	64.29	72.89	87.64	95.75	99.53

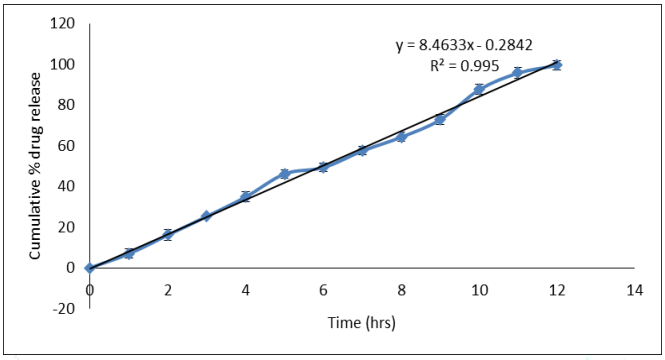

Figure 1: Zero order release kinetics model of controlled release ocusert of Sulfacetamide sodium containing PVA, EC and HPMC (F9).

Sterility studies

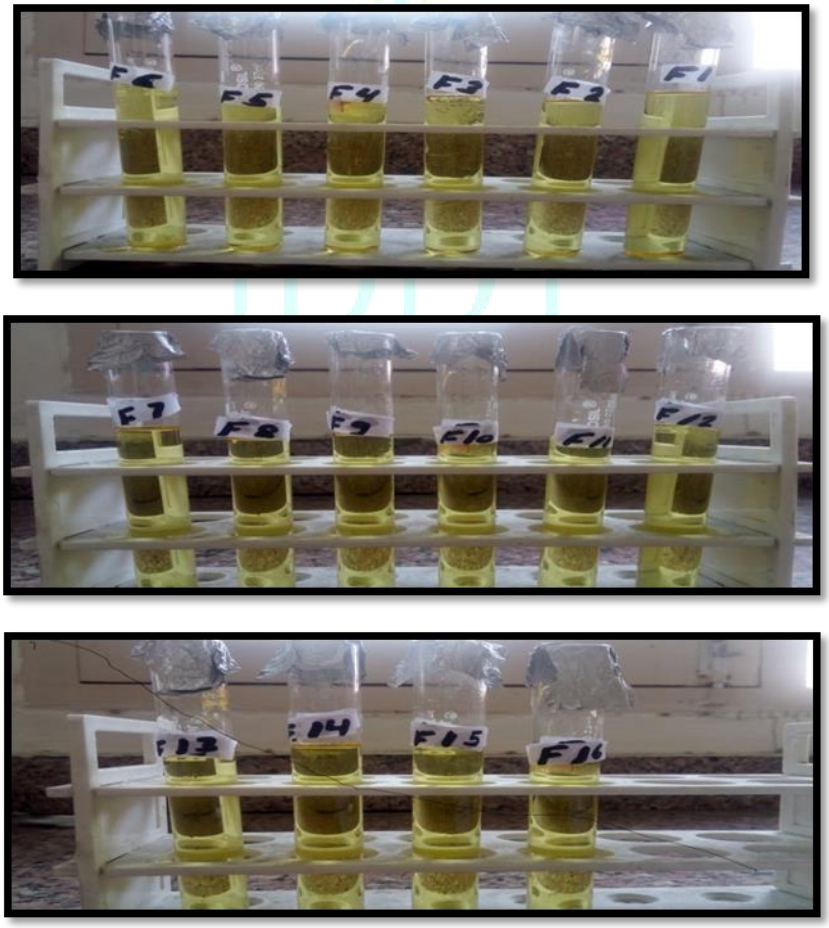

Figure 2: Sterility test for Sulfacetamide sodium in soybean casein media

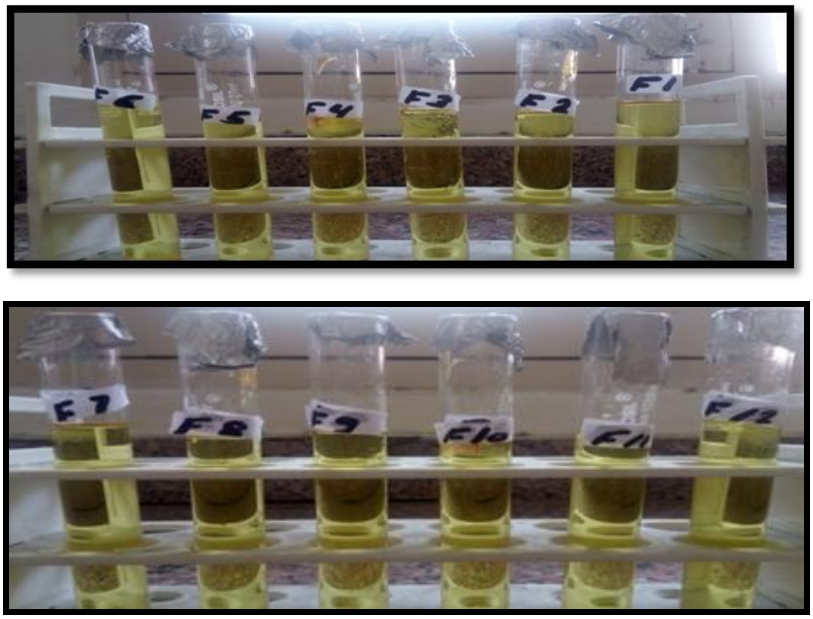

Figure 3: Sterility test for Sulfacetamide sodium in Fluid thioglycolate media

There was no appearance of turbidity and hence no evidence of microbial growth when the formulation was incubated for not less than 14 days at 300°C to 350°C in case of fluid thioglycolate medium (Figure 2) and at 20°C to 25°C in case of soybean casein digest medium (Figure 3) the formulation being examined there for passed the test for sterility.

CONCLUSION

Ocular inserts of Sulfacetamide sodium were prepared successfully by solvent casting method using different polymers (PVA, HPMC and EC) in different combinations and proportions. Di-butyl-phthalate was used as plasticizer. Methyl-paraben and Propyl-paraben were used as preservatives and monobasic sodium phosphate was used as buffer. Resultant formulation F9 showed best *in-vitro* release of Sulfacetamide sodium. We found PVA and HPMC were good film forming hydrophilic polymers and a promising agent for ocular delivery. EC was a satisfactory polymeric ingredient to fabricate the rate controlling membrane of the ocusert system. Di-butyl-phthalate enhanced the permeability of Sulfacetamide sodium and thus therapeutic levels of drug could be achieved.

These ocuserts were smooth, flexible, and uniform in thickness and weight. The ocusert showed sustained release characteristics with a zero order of drug release; so prepared ocusert could be a promising delivery system for Sulfacetamide sodium with controlled drug release profile. Sterility studies was done and it was found no appearance of turbidity and hence no evidence of microbial growth. Overall, all the problems of poor bioavailability, frequent dosing and wastage of active ingredient were successfully dealt with developed ocular insert.

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